

# **EXHIBIT A132**

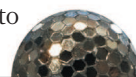
# THIS WEEK

## EDITORIALS

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## Significant debate

*Looking beyond statistical significance would make science harder, but might help to avoid false positives, overhyped claims and overlooked effects.*

Fans of *The Hitchhiker's Guide to the Galaxy* know that the answer to life, the Universe and everything is 42. The joke, of course, is that truth cannot be revealed by a single number.

And yet this is the job often assigned to *P* values: a measure of how surprising a result is, given assumptions about an experiment, including that no effect exists. Whether a *P* value falls above or below an arbitrary threshold demarcating 'statistical significance' (such as 0.05) decides whether hypotheses are accepted, papers are published and products are brought to market. But using *P* values as the sole arbiter of what to accept as truth can also mean that some analyses are biased, some false positives are overhyped and some genuine effects are overlooked.

Change is in the air. In a Comment on page 305, three statisticians call for scientists to abandon statistical significance. The authors do not call for *P* values themselves to be ditched as a statistical tool — rather, they want an end to their use as an arbitrary threshold of significance. More than 800 researchers have added their names as signatories. A series of related articles is being published by the American Statistical Association this week (R. L. Wasserstein *et al. Am. Stat.* <https://doi.org/10.1080/00031305.2019.1583913>; 2019). "The tool has become the tyrant," laments one article.

Statistical significance is so deeply integrated into scientific practice and evaluation that extricating it would be painful. Critics will

counter that arbitrary gatekeepers are better than unclear ones, and that the more useful argument is over which results should count for (or against) evidence of effect. There are reasonable viewpoints on all sides; *Nature* is not seeking to change how it considers statistical analysis in evaluation of papers at this time, but we encourage readers to share their views (see [go.nature.com/correspondence](https://go.nature.com/correspondence)).

If researchers do discard statistical significance, what should they do instead? They can start by educating themselves about statistical misconceptions. Most important will be the courage to consider uncertainty from multiple angles in every study. Logic, background knowledge and experimental design should be considered alongside *P* values and similar metrics to reach a conclusion and decide on its certainty.

When working out which methods to use, researchers should also focus as much as possible on actual problems. People who will duel to the death over abstract theories on the best way to use statistics often agree on results when they are presented with concrete scenarios.

Researchers should seek to analyse data in multiple ways to see whether different analyses converge on the same answer. Projects that have crowdsourced analyses of a data set to diverse teams suggest that this approach can work to validate findings and offer new insights.

In short, be sceptical, pick a good question, and try to answer it in many ways. It takes many numbers to get close to the truth. ■

## Desperate steps

*The decision to spray citrus orchards with antibiotics is based on scant evidence.*

The past ten years have seen many positive moves to curb the liberal use of antibiotics in agriculture. Authorities in the United States and the European Union have banned the use of medically important antibiotics as growth promoters in some livestock, and the meat industry has been scaling back its purchases of these drugs. The shift is propelled by both consumer demand and mounting evidence that using antibiotics recklessly can facilitate the spread of drug resistance in human pathogens.

A 2018 report on antimicrobial resistance in the environment (see [go.nature.com/2tbv6hi](https://go.nature.com/2tbv6hi)) identified another potential concern: spraying crops with antibiotics to fight plant pathogens.

The technique has been used in a limited way to fight the bacterial disease fire blight in apple and pear orchards, and since 2016 has been deployed in emergency applications for the disease known as citrus greening or huanglongbing. This month, the US Environmental Protection Agency is in the final stages of approving a huge ramp-up in spraying of two human antibiotics, streptomycin and oxytetracycline,

on citrus groves in Florida and California (see page 302).

It is a desperate act. Citrus greening, a bacterial disease spread by an invasive insect known as a citrus psyllid (*Diaphorina citri*), threatens to completely destroy the orange industry in Florida, which adds some US\$8.6 billion to the economy. By some estimates, up to 90% of trees in the state have been infected and will eventually die.

Spraying does not eradicate the disease. It might help growers eke out a few more years of profit from existing trees, but even evidence for this is thin. Whether the drugs will lead to antibiotic resistance in the bacteria that cause greening — as has happened in the pathogen that causes fire blight — is also unclear. And the effects on the trees' communities of microorganisms, or microbiota, that might promote growth and protect trees from disease have not been studied closely in published reports.

More worrying from a public-health perspective is whether the spraying will lead to the evolution and spread in soil microbes of resistance genes that could eventually show up in human pathogens. Although some industry-sponsored studies have looked at the potential benefits and risks of antibiotic spraying, the dearth of publicly available data is alarming, particularly in the face of a massive scale-up in application that could set a global precedent.

The situation for the citrus industry is serious, and the desire to act understandable, but it is premature to throw antibiotics at the problem. If spraying does move ahead, which seems inevitable, it must be accompanied by independent research. The public deserves close accounting of the environmental effects and the potential impacts on public health. ■